

# Does setting the breathing machine (ventilator) to deliver breaths using a method called airway pressure release ventilation help patients with diseased lungs to heal faster and spend less time on a ventilator?

<b>Submission date</b> 12/06/2024	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 21/06/2024	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 12/09/2025	<b>Condition category</b> Respiratory	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Around half of all patients in critical care need help from a breathing machine (ventilator) to maintain oxygen levels. Although they may be life-saving, breathing machines can cause damage to diseased lungs and make chest infections more likely.

The usual way a breathing machine is used aims to protect the lungs from damage until they are healed. However, damage can still occur, and the lungs take time to recover. Airway pressure release ventilation (APRV) is a way of using the breathing machine that we think causes less damage. It moves gas into the lungs gently over a longer time. This helps to reduce lung damage, helping faster healing. APRV may reduce time on the breathing machine and in the hospital which may save costs. APRV may also reduce the risk of death.

The aim of this study is to find out if setting the breathing machine to deliver breaths using APRV helps patients with diseased lungs to heal faster and spend less time on a ventilator compared to the usual way breathing support is given in critical care. The researchers also want to know if APRV saves more lives, improves quality of life, and saves the NHS money by helping people leave CCU sooner.

### Who can participate?

Patients admitted to a CCU in the UK who are:

1. Aged 18 years or more
2. Receiving support from a breathing machine
3. Have moderate to severely low oxygen levels
4. Are expected by the critical care team to stay on a breathing machine for more than 2 days

### What does the study involve?

Participants will be assigned by chance (randomised) to one of two groups.

1. APRV: The breathing machine will be set to the APRV mode. APRV moves gas into the lungs

gently over a longer time. APRV is available on all ventilators that are used within the NHS.

2. Usual care: The breathing machine will be set as usual by the critical care team.

There will be no other changes to care delivered by the critical care team for patients in both the APRV and usual care group.

Participants, the research team, or the critical care team will not be able to choose which group your relative/friend is in. This is decided by a computer at random, just like tossing a coin or drawing lots.

The research team will collect information about the care the participants receive while in critical care including how the breathing machine is used, how long they need the machine, and how long they stay in critical care. The research team will collect the participants' personal information such as age, ethnicity, sex and past medical conditions before coming to critical care as this helps them to understand the effect of APRV on different groups of people.

After leaving the hospital, participants will be sent a questionnaire 2 and 6 months after hospital discharge asking about their overall wellbeing and quality of life. Each questionnaire will take about 5 to 10 minutes to complete. If needed, someone can complete them on the participant's behalf. The researchers will share the participant's name, email address, and phone number with a third-party company in order to send them the questionnaires by text message or email. They may also get in touch with participants by text message or email if we have any queries about their questionnaire or if we have any updates related to the study.

What are the possible benefits and risks of participating?

As this is a study, participants may or may not benefit from taking part. However, the findings of the research will help to improve the treatments and care provided to patients with a similar condition now and in the future.

There is no payment for taking part in this study. However, to thank participants for their time in completing the follow-up questionnaires at 2 and 6 months, they will be given a small monetary gift voucher alongside each questionnaire.

The University of Warwick is currently leading several studies looking at how we treat patients with respiratory failure. This group of studies is called the 'Confederation of Respiratory Critical Care Trials' or 'CoReCCT'. If participants are taking part in other studies within CoReCCT, they will not need to complete questionnaires for each study. Participants will only be asked to complete the questionnaires once and will receive one voucher with each questionnaire.

At this time, there are no important disadvantages or risks to taking part.

Where is the study run from?

Warwick University in partnership with NHS hospitals across the UK

When is the study starting and how long is it expected to run for?

January 2024 to August 2027

Who is funding the study?

National Institute for Health Research, Health Technology Assessment (NIHR154501) (UK)

Who is the main contact?

RELEASE trial manager, [RELEASE@warwick.ac.uk](mailto:RELEASE@warwick.ac.uk)

## Contact information

Type(s)

Scientific, Principal investigator

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**Contact name**

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**Type(s)**

Public, Scientific

**Contact name**

Mr Jonathan Guck

**Contact details**

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# Additional identifiers

## Clinical Trials Information System (CTIS)

Nil known

## Integrated Research Application System (IRAS)

335630

## ClinicalTrials.gov (NCT)

Nil known

## Protocol serial number

IRAS 335630, NIHR154501, CPMS 62929

# Study information

## Scientific Title

Airway Pressure Release Ventilation (APRV) vs conventional ventilation for patients with moderate to severe acute hypoxemic respiratory failure: the RELEASE trial

## Acronym

RELEASE

## Study objectives

What is the clinical and cost-effectiveness of airway pressure release ventilation (APRV) for adults requiring invasive mechanical ventilation (IMV) for moderate-severe acute hypoxaemic respiratory failure (AHRF)?

## Ethics approval required

Ethics approval required

## Ethics approval(s)

1. approved 08/07/2024, Wales REC 2 (The Cardiff North Inn by Accor, Circle Way East, Llanadern, Cardiff, CF23 9XF, United Kingdom; +44 (0)2922941119; Wales.REC2@wales.nhs.uk), ref: 24/WA/0128

2. submitted 18/06/2025, Scotland A REC (NHS Lothian , Edinburgh, EH1 3EG, United Kingdom; +44 131 465 5680; Manx.Neill@nhslothian.scot.nhs.uk), ref: 25-SS-0056-IRAS-351070

## Study design

Multi-centre randomized allocation-concealed controlled open-label pragmatic parallel-group clinical and cost-effectiveness trial with an internal pilot

## Primary study design

Interventional

## Study type(s)

Treatment

## Health condition(s) or problem(s) studied

Moderate to severe acute hypoxaemic respiratory failure (AHRF)

## **Interventions**

Participants are randomised to either:

1. Early airway pressure release ventilation (APRV)
2. Standard conventional lung protective invasive mechanical ventilation (no APRV)

Participants will be randomised via randomly permuted blocks using an automated web-based system on a one-to-one basis, stratified by site and prior enrolment into the Awake Prone Positioning and Protect Airways trials, using a computer-generated randomisation schedule managed by the Warwick CTU. The researchers have selected a parallel group RCT design to minimise selection bias and ensure against accidental bias.

The intervention (APRV or control) will continue until one of the following criteria is met:

1. 60 days after randomisation
2. Successful unassisted breathing (at 48 hours with no further requirement for inspiratory support or extracorporeal lung support. See section 2.4.3 for the full definition)
3. Trial intervention-related serious adverse event
4. Death or discontinuation of active treatment
5. Withdrawal of consent

## **Intervention Type**

Other

## **Primary outcome(s)**

Current primary outcome measure as of 25/06/2025:

Duration of mechanical ventilation (defined as the time from randomisation to first successful unassisted breathing or death) measured using data collected from site staff at the time of first successful unassisted breathing or death

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Previous primary outcome measure:

Duration of invasive mechanical ventilation (defined as the time from randomisation to first successful unassisted breathing or death) measured using data collected from site staff at the time of first successful unassisted breathing or death

## **Key secondary outcome(s)**

Current secondary outcome measures as of 25/06/2025:

1. All-cause mortality measured using data collected from site staff at 2 and 6 months
2. Time to first successful extubation
3. Need for reintubation prior to achieving first successful unassisted breathing
4. Use of non-invasive ventilation following extubation but prior to achieving first successful unassisted breathing
5. CCU and hospital length of stay measured using data collected from site staff at time of CCU and hospital discharge
6. Serious adverse events measured using data collected from site staff up to time of hospital discharge

7. Health-related quality of life measured using the 5-level EQ-5D version (EQ-5D-5L) at 2 and 6 months
8. Acute health care use measured using participant-completed resource use questionnaires and, if available, enriched using data obtained from site staff or linkage at 2 and 6 months
9. Within-trial cost-utility analysis from an NHS hospital care perspective using data collected from site staff and data obtained through linkage to routine datasets at 2 and 6 months

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Previous secondary outcome measures:

1. All-cause mortality measured using data collected from site staff at 2 and 6 months
2. Time to first extubation measured using data collected from site staff at time of extubation
3. Reintubation measured using data collected from site staff at time of reintubation
4. Use of non-invasive ventilation following extubation measured using data collected from site staff at time of extubation
5. CCU and hospital length of stay measured using data collected from site staff at time of CCU and hospital discharge
6. Serious adverse events measured using data collected from site staff up to time of hospital discharge
7. Health-related quality of life measured using the 5-level EQ-5D version (EQ-5D-5L) at 2 and 6 months
8. Acute health care use measured using participant-completed resource use questionnaires and, if available, enriched using data obtained from site staff or linkage at 2 and 6 months
9. Within-trial cost-utility analysis from an NHS hospital care perspective using data collected from site staff and data obtained through linkage to routine datasets at 2 and 6 months

### **Completion date**

31/08/2027

## **Eligibility**

### **Key inclusion criteria**

Current inclusion criteria as of 25/06/2025:

1. Age  $\geq 18$  years
2. Receiving invasive mechanical ventilation
3. Moderate to severe acute hypoxaemic respiratory failure, defined as a single measurement showing a  $\text{PaO}_2/\text{FiO}_2$  ratio  $< 20$  kPa while receiving a Positive End-Expiratory Pressure (PEEP) of  $\geq 5$  cmH<sub>2</sub>O, assessed at any point within the first 60 hours after the initiation of invasive mechanical ventilation
4. Expected to stay on invasive mechanical ventilation for  $> 48$  hours

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Previous inclusion criteria:

1. Age  $\geq 18$  years
2. Receiving invasive mechanical ventilation
3. Moderate to severe AHRF ( $\text{PaO}_2/\text{FiO}_2 < 20$  kPa with Positive End Expiratory Pressure (PEEP)  $\geq 5$  cmH<sub>2</sub>O) assessed at the time of screening (or as documented in the medical record in the

preceding 2 hours)

4. Expected to stay on invasive mechanical ventilation for >48 hours

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

### **Sex**

All

### **Key exclusion criteria**

Current exclusion criteria as of 25/06/2025:

1. Receiving IMV  $\geq 60$  hours at the time of screening as will be unable to deliver early APRV
  2. Primary reason for invasive mechanical ventilation is one of the following:
    - 2.1. Asthma
    - 2.2. Severe COPD
    - 2.3. Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue)
    - 2.4. Existing neuromuscular disease such as motor neurone disease, Guillain Barre or myasthenia gravis (as the cause of respiratory failure is not primarily lung-related)
  3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs)\*
  4. Severe hypercapnic respiratory acidosis (pH < 7.20 on the arterial blood gas assessed for trial inclusion)\*
  5. Ongoing air leak (e.g. unresolved pneumothorax at time of screening)\*
  6. Traumatic brain injury with uncontrolled intracranial hypertension\*
  7. Likely death or treatment withdrawal in the next 24 hours
  8. Home ventilation or home oxygen therapy prior to admission
  9. Receiving, or decision to commence, ECMO in the next 24 hours
- \*(patients can be recruited if this resolves and remain eligible)

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Previous exclusion criteria:

1. Receiving IMV  $\geq 60$  hours at the time of screening as will be unable to deliver early APRV
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  - 2.1. Asthma
  - 2.2. Severe COPD
  - 2.3. Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue)
  - 2.4. Existing neuromuscular disease such as motor neurone disease, Guillain Barre or myasthenia

gravis (as the cause of respiratory failure is not primarily lung-related)

3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs)\*

4. Severe hypercapnic respiratory acidosis (pH <7.20 on the arterial blood gas assessed for trial inclusion)\*

5. Ongoing air leak (e.g. unresolved pneumothorax at time of screening)\*

6. Traumatic brain injury with uncontrolled intracranial hypertension\*

7. Likely death or treatment withdrawal in the next 24 hours

8. Home ventilation or home oxygen therapy prior to admission

\*(patients can be recruited if this resolves and remain eligible)

#### **Date of first enrolment**

14/02/2025

#### **Date of final enrolment**

31/05/2027

## **Locations**

#### **Countries of recruitment**

United Kingdom

England

Northern Ireland

Scotland

Wales

#### **Study participating centre**

**Guy's and St Thomas' NHS Foundation Trust**

St Thomas' Hospital

Westminster Bridge Road

London

United Kingdom

SE1 7EH

#### **Study participating centre**

**Arrow Park Hospital**

Arrowe Park Hospital

Arrowe Park Road

Wirral

United Kingdom

CH49 5PE

**Study participating centre**  
**Bedford Hospital**  
Icash Bedford Hospital  
Kempston Road  
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MK42 9DJ

**Study participating centre**  
**University Hospital Bristol**  
Bristol Royal Infirmary  
Marlborough Street  
Bristol  
United Kingdom  
BS2 8HW

**Study participating centre**  
**Conquest Hospital**  
The Ridge  
St. Leonards-on-sea  
United Kingdom  
TN37 7RD

**Study participating centre**  
**Queen Alexandras Hospital**  
Southwick Hill Road  
Cosham  
Portsmouth  
United Kingdom  
PO6 3LY

**Study participating centre**  
**Tameside General Hospital**  
Fountain Street  
Ashton-under-lyne  
United Kingdom  
OL6 9RW

**Study participating centre**

**Blackpool Teaching Hospitals NHS Foundation Trust**

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Whinney Heys Road  
Blackpool  
United Kingdom  
FY3 8NR

**Study participating centre**

**Ipswich Hospital Utc**

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Heath Road  
Ipswich  
United Kingdom  
IP4 5PD

**Study participating centre**

**James Cook University Hospital**

Marton Road  
Middlesbrough  
United Kingdom  
TS4 3BW

**Study participating centre**

**Kingston Hospital**

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KT2 7QB

**Study participating centre**

**Medway NHS Foundation Trust**

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Gillingham  
United Kingdom  
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**Study participating centre**

**Russells Hall Hospital**

Pensnett Road  
Dudley

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**Study participating centre**  
**Queen Elizabeth Hospital Lewisham**  
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SE18 4QH

**Study participating centre**  
**St Georges Hospital**  
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**Study participating centre**  
**Aintree University Hospital**  
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**Study participating centre**  
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**Study participating centre**  
**University Hospital of North Tees**  
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United Kingdom  
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**Study participating centre**

**William Harvey Hospital**

Kennington Road  
Willesborough  
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United Kingdom  
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**Study participating centre**

**Milton Keynes University Hospital**

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Eaglestone  
Milton Keynes  
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**Study participating centre**

**University Hospitals Plymouth NHS Trust**

Derriford Hospital  
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PL6 8DH

**Study participating centre**

**Countess of Chester Hospital**

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Liverpool Road  
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**Study participating centre**

**Darent Valley Hospital**

Darenth Wood Road  
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**Study participating centre**  
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**Study participating centre**  
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B66 2QT

**Study participating centre**  
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CF72 8XR

**Study participating centre**  
**University College London Hospitals NHS Foundation Trust**  
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**Study participating centre**  
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The Whittington Hospital  
Magdala Avenue  
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## **Sponsor information**

**Organisation**

University of Warwick

ROR

<https://ror.org/01a77tt86>

# Funder(s)

Funder type

Government

Funder Name

Health Technology Assessment Programme

Alternative Name(s)

NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

# Results and Publications

Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Participant information sheet</a>			25/06/2025	No	Yes
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes
<a href="#">Protocol file</a>	version 2.0	13/06/2024	16/07/2024	No	No
<a href="#">Protocol file</a>	version 3.0	26/03/2025	25/06/2025	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes